# The effects of dutasteride or tamsulosin alone and in combination on storage and voiding symptoms in men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH): 4-year data from the Combination of Avodart and Tamsulosin (CombAT) study

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Level of Evidence 1b

**What's known on the subject? and What does the study add?**
Long-term treatment with combination therapy (dutasteride plus tamsulosin) is significantly superior to tamsulosin but not dutasteride at reducing the relative risk of AUR or BPH-related surgery. Furthermore, combination therapy is significantly superior to both monotherapies at reducing the relative risk of BPH clinical progression, and provides significantly greater reductions in IPSS. In addition, combination therapy significantly improves patient-reported, disease specific QoL and treatment satisfaction compared with either monotherapy. Two-year results from the CombAT study showed that combination therapy was more effective than either monotherapy in controlling both storage and voiding symptoms, irrespective of baseline prostate volume (for men with prostate volume ≥30 cc). This *post-hoc* two-year analysis also showed that treatment with dutasteride not only improved voiding symptoms, as would be expected from its effects on prostate volume, but was also as effective as the α-blocker tamsulosin in the control of storage symptoms.

## OBJECTIVE

- To assess the effects of combined therapy with dutasteride and tamsulosin on voiding and storage symptoms compared with those of dutasteride or tamsulosin alone, using 4-year data from the Combination of Avodart and Tamsulosin (CombAT) study.

## PATIENTS AND METHODS

- Men ($n = 4844$) aged ≥50 years with moderate-to-severe lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH), a prostate volume of ≥30 mL, and a serum prostate-specific antigen level of 1.5–10 ng/mL.
- CombAT was a multicentre, double-blind, parallel-group study.
- Oral dutasteride (0.5 mg) or tamsulosin (0.4 mg) alone or in combination was taken daily for 4 years.
- Mean changes from baseline in storage and voiding symptoms at 4 years were assessed using subscales of the International Prostate Symptom Score.

## RESULTS

- At 4 years, the mean reduction in the storage subscore was significantly greater in the combined therapy group vs the dutasteride (adjusted mean difference –0.43) and tamsulosin (adjusted mean difference –0.96) monotherapy groups ($P < 0.001$).
- Also at 4 years, the mean reduction in the voiding subscore was significantly greater in the combined therapy group vs the dutasteride (adjusted mean difference –0.51) and tamsulosin (adjusted mean difference –1.60) monotherapy groups ($P < 0.001$).
- The improvement in the storage subscore with combined therapy was significantly better ($P < 0.001$) than dutasteride and tamsulosin from 3 months and 12 months, respectively. Similarly, the improvement in the voiding subscore with combined therapy was significantly better than dutasteride ($P < 0.001$) and tamsulosin ($P \leq 0.006$) from 3 months and 6 months, respectively.
- Improvements in the storage and voiding symptom subscores with combined therapy were achieved irrespective of prostate volume, although in men with the highest baseline prostate volumes (≥58 mL),

combined therapy was not better than dutasteride.

## CONCLUSIONS

- In men with a prostate volume of ≥30 mL, combined therapy with dutasteride plus tamsulosin provided better long-term (up to 4 years) control of both storage and voiding LUTS compared with tamsulosin monotherapy.
- Combined therapy was better than dutasteride monotherapy in men with prostate volumes of ≥30 to <58 mL, but not in men with a prostate volume of ≥58 mL.

## KEYWORDS

benign prostatic hyperplasia, CombAT, urinary symptoms, dutasteride, tamsulosin, combined therapy

## INTRODUCTION

Male LUTS can be categorised as voiding and post-voiding symptoms (associated with the passage of urine), and storage symptoms (associated with urine storage in the bladder) [1]. Voiding symptoms include reduced stream, intermittency, hesitancy, straining and incomplete bladder emptying, and are due to development of urethral obstruction, often as a result of benign prostatic enlargement (BPE) secondary to BPH [2,3]. Post-voiding symptoms such as dribbling are currently incompletely assessed in standardised health questionnaires. Storage symptoms include frequency, nocturia, urgency and urinary incontinence. They are commonly seen in overactive bladder (OAB) and BPE, and are thought to arise from altered smooth muscle structure and function in the bladder and prostate [3,4]. Storage symptoms tend to be more common than voiding symptoms [5], and studies indicate that storage symptoms are also more bothersome [6,7].

Several options exist for the management of LUTS, and the selection of pharmacological treatments usually relates to the underlying pathophysiology. Symptoms of OAB are most often treated with anti-muscarinic agents that directly block $M_2$ and $M_3$ receptors and reduce cholinergic innervation of bladder detrusor muscle [8]. BPE symptoms can be relieved with α-blockers, which inhibit sympathetic stimulation via $\alpha_1$-adrenoceptors, thereby relaxing smooth muscle in the bladder neck, prostate and bladder detrusor [9–11]. Although α-blockers provide rapid relief from LUTS secondary to BPE, these agents do not reduce prostate volume or interfere with the natural history of prostate growth over time [12]. Not all BPE is associated with LUTS, and men without BPE can also develop LUTS that are responsive to α-blocker therapy [13,14].

In men with moderate-to-severe LUTS and an enlarged prostate, 5α-reductase inhibitors (5ARIs) are a recommended treatment option [15]. 5ARIs reduce prostate volume and decrease urethral obstruction, providing continual symptom improvement and reducing the risk of acute urinary retention (AUR) and the need for BPH-related surgery [12]. Combined therapy with an α-blocker and a 5ARI has also been shown to effectively treat LUTS due to BPH [2,16,17]. In a *post hoc* analysis of the 2-year results from the CombAT study, combined therapy was more effective than either monotherapy in controlling both storage and voiding symptoms, irrespective of baseline prostate volume (for men with a prostate volume of ≥30 mL) [18]. Interestingly, this *post hoc* 2-year analysis of the CombAT study also showed that treatment with dutasteride not only improved voiding symptoms, as would be expected from its effects on prostate volume, but was also as effective as the α-blocker tamsulosin in the control of storage symptoms [7].

Here we present the findings of a *post hoc* analysis of storage and voiding symptoms from CombAT performed at the end of the study (4 years).

## PATIENTS AND METHODS

The rationale and design of the CombAT study have been described in detail previously [19]. Briefly, the study evaluated the efficacy and safety of combining the dual 5ARI dutasteride and the α-blocker tamsulosin in men with moderate-to-severe LUTS due to BPH (IPSS of ≥12) at increased risk of disease progression (age ≥50 years, prostate volume ≥30 mL, serum PSA level 1.5–10 ng/mL and maximum urinary flow rate 5–15 mL/s with minimum voided volume ≥125 mL). Exclusion criteria included history or evidence of prostate cancer, history of prostatic surgery or other invasive procedures to treat BPH, and occurrence of AUR within 3 months of study entry. After screening, all eligible patients were entered into a single-blind run-in period during which they received dutasteride and tamsulosin placebos for 4 weeks. All subjects were then randomized in a 1:1:1 ratio to receive once-daily treatment with 0.5 mg dutasteride plus 0.4 mg tamsulosin, 0.5 mg dutasteride plus tamsulosin-matched placebo, or 0.4 mg tamsulosin plus dutasteride-matched placebo for 4 years. Patients self-administered study treatments and returned to the clinic for assessments every 3 months.

Separate primary and secondary endpoints were analysed at 2 and 4 years [19]. The primary endpoint for the pre-planned analysis at 2 years was the mean change from baseline in IPSS. Secondary endpoints at 2 years included the total change in prostate volume from baseline. At 4 years, the primary endpoint was the time to first event of AUR or BPH-related prostatic surgery, with the proportion of subjects with AUR or undergoing BPH-related prostate surgery acting as a supportive endpoint to the primary analysis [16]. Secondary endpoints at 4 years included all 2-year primary and secondary endpoints and so IPSS data were collected for the duration of the study. The IPSS comprises eight questions, seven of which (1–7) relate to symptom type and severity. Symptom severity is scored on a scale of 0 (least severe) to 5 (most severe). The seven symptom questions can be validly separated into a three-item storage subscale (0–15 points) comprised of questions relating to frequency, urinary incontinence, and nocturia, and a four-item voiding subscale of 0–20 points comprised of questions relating to incomplete emptying, hesitancy, weak stream and straining [20].

Data were analysed for the intention-to-treat population, which comprised all patients who were randomized into the double-blind treatment groups after the 4-week placebo run-in period. In the present *post hoc* 4-year analysis, the mean changes from baseline in IPSS storage and voiding subscales were summarised by treatment group using the last-observation-carried-forward approach. The mean changes in storage and voiding subscores were determined at each follow-up assessment using a general linear model with adjustments for treatment, investigative site cluster and baseline IPSS (storage or voiding). Pairwise treatment comparisons from the general linear model were carried out at $\alpha = 0.05$. These analyses were conducted outside of the protocol-specified endpoint hierarchy, with no formal adjustments for multiplicity of tests. For the present analyses, comparisons of combined therapy vs each monotherapy, and of dutasteride monotherapy vs tamsulosin monotherapy, were performed. These comparisons were performed for all patients and for patients in each of the following prostate volume tertiles: 30 to <42 mL, 42 to <58 mL and ≥58 mL. These tertiles were calculated based on baseline prostate volume measurements such that one-third of subjects were included in each. Data are presented as the mean (SEM), unless otherwise stated.

## RESULTS

In all, 4844 men were randomized to treatment in CombAT, with 3195 (66%) completing the 4-year visit. There was a higher rate of discontinuations in the tamsulosin group (39%) compared with the combined therapy and dutasteride groups (31% and 33%, respectively) [16]. Overall, baseline characteristics were similar between the three treatment groups [16]. Of note for the present analyses, the mean (SD) IPSS storage subscores at baseline were comparable between treatment groups [7.3 (3.0) in the combined therapy, 7.2 (2.9) in the dutasteride and 7.2 (2.9) in the tamsulosin groups]. The mean (SD) IPSS voiding subscores were also similar across treatment groups [9.3 (4.4) in the combined therapy, 9.2 (4.3) in the dutasteride and 9.2 (4.2) in the tamsulosin groups].

### IPSS STORAGE SUBSCORES

Combined therapy (dutasteride plus tamsulosin) was associated with a significantly greater mean reduction in IPSS storage subscore at 4 years than either dutasteride or tamsulosin alone ($P < 0.001$ for both comparisons; Fig. 1). The mean IPSS storage subscores decreased in all treatment groups soon after treatment initiation (Fig. 2). The reduction in storage subscore with combined therapy was significantly better than dutasteride from 3 months onwards ($P < 0.001$), and significantly better than tamsulosin from 12 months onwards ($P < 0.001$; Fig. 2). At 4 years, the mean reductions in the scores for each individual storage question of the IPSS (questions 2, 4 and 7) were significantly greater with combined therapy than with either monotherapy ($P \leq 0.008$). Also at 4 years, there was a significant ($P < 0.001$) correlation between changes in storage symptoms and changes in health-related quality of life (HRQL) as assessed by IPSS question 8, with a Pearson correlation of 0.52.

Comparison of data from the two monotherapy groups showed that tamsulosin was associated with a significantly greater mean reduction in IPSS storage subscore than dutasteride over the first 9 months of the study (at 3, 6 and 9 months; $P \leq 0.004$). Although, there were no significant differences in this variable between the two monotherapy groups from 12–27 months, the mean reduction in storage subscore was significantly greater with dutasteride than with tamsulosin from 27 months onwards ($P \leq 0.009$).

### IPSS VOIDING SUBSCORES

Combined therapy produced a significantly greater mean reduction in the IPSS voiding subscore at 4 years than either dutasteride or tamsulosin monotherapy ($P < 0.001$ for both; Fig. 1). As for the IPSS storage scores, the mean IPSS voiding subscores began to decrease in all treatment groups shortly after initiation of treatment (Fig. 3). The reduction in the voiding subscore with combined therapy was significantly better than dutasteride alone from 3 months ($P < 0.001$), and tamsulosin from 6 months ($P \leq 0.006$; Fig. 3). For three of the four individual voiding questions of the IPSS (questions 1, 3, and 5), the mean score reductions at 4 years were significantly greater with combined therapy than with either monotherapy ($P \leq 0.005$); for IPSS question 6 (straining), the mean score reduction with combined therapy was significantly greater compared with tamsulosin ($P < 0.001$) but not compared with dutasteride ($P = 0.12$) monotherapy. Also at 4 years, there was a significant ($P < 0.001$) correlation between changes in voiding symptoms and changes in HRQL (IPSS question 8), with a Pearson correlation of 0.56.

*FIG. 1. The mean changes from baseline in IPSS at 4 years (total score, storage subscore and voiding subscore).*

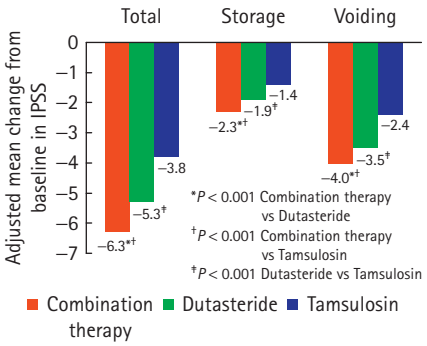



*FIG. 2. The mean changes from baseline in IPSS storage subscores.*

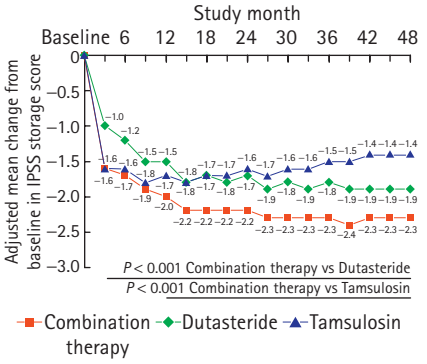



*FIG. 3. The mean changes from baseline in IPSS voiding subscores.*

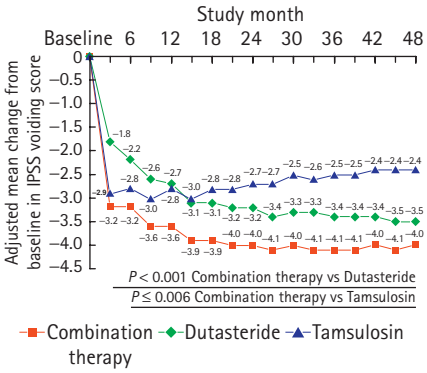
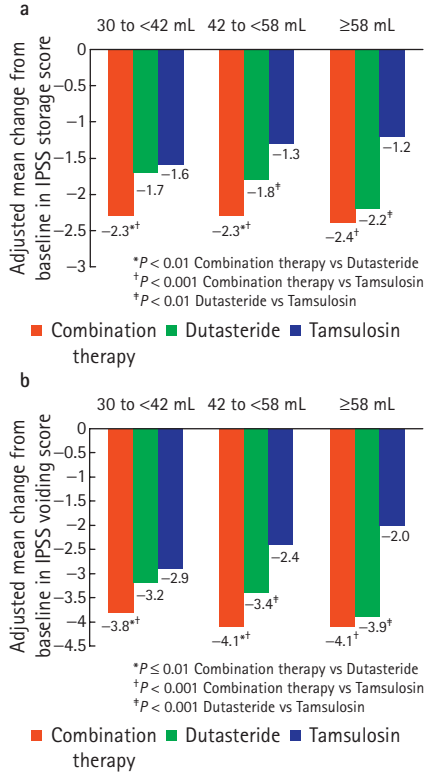


*FIG. 4. The mean changes from baseline in IPSS storage (**a**) and voiding (**b**) subscores at 4 years by baseline prostate volume.*




Comparison of the IPSS voiding subscores for the two monotherapy groups showed a trend similar to that for the IPSS storage subscores. Tamsulosin monotherapy was associated with a greater mean reduction in IPSS voiding subscore than dutasteride monotherapy over the first 9 months of the study (3, 6 and 9 months; $P \leq 0.003$). However, between 12 and 18 months, there were no significant differences between the dutasteride and tamsulosin groups. From 18 months onwards, the mean reduction in voiding subscore was significantly greater with dutasteride than with tamsulosin monotherapy ($P \leq 0.018$).

### IPSS STORAGE AND VOIDING SUBSCORES BY BASELINE PROSTATE VOLUME

In men with baseline prostate volumes in the lowest tertile (30 to <42 mL), the mean reduction in both IPSS storage and voiding subscores at 4 years was significantly greater with combined therapy than with either dutasteride or tamsulosin alone ($P \leq 0.01$; Fig. 4a,b). There was no significant difference between the dutasteride and tamsulosin groups in either storage or voiding subscores.

In men with baseline prostate volumes in the middle tertile (42 to <58 mL), the mean reduction in both IPSS storage and voiding subscores at 4 years was also significantly greater with combined therapy than with either dutasteride or tamsulosin alone ($P \leq 0.01$; Fig. 4a,b). In addition, the mean reduction in both subscores with dutasteride was significantly greater than with tamsulosin monotherapy ($P < 0.01$).

In men with a baseline prostate volume in the highest tertile (≥58 mL), the mean reduction in storage and voiding subscores at 4 years in the combined therapy group was significantly greater than that in the tamsulosin monotherapy group ($P < 0.001$). However, there were no statistically significant differences in these subscores between the combined therapy and dutasteride groups in this tertile (Fig. 4a,b). Also, the mean reduction in both subscores with dutasteride was significantly greater than with tamsulosin monotherapy ($P < 0.001$).

At 48 months, there was a statistically significant ($P \leq 0.01$) difference between the combined therapy group and each monotherapy group in terms of HRQL (IPSS question 8) in the lower two prostate volume tertiles. In the highest prostate volume tertile, there was a significant difference between the combined therapy and the tamsulosin monotherapy groups ($P < 0.001$), but not between the combined therapy and dutasteride monotherapy groups ($P = 0.065$).

## DISCUSSION

The present *post hoc* analysis of the CombAT study showed that combined therapy with dutasteride plus tamsulosin provided significantly greater improvements in both storage and voiding symptoms compared with dutasteride or tamsulosin alone after 4 years. There were greater improvements in responses to all IPSS questions relating to storage with combined therapy than with either monotherapy. Similarly, combined therapy was associated with improved responses to three of four IPSS voiding questions (relating to incomplete emptying, hesitancy, and weak stream); responses to a fourth voiding question regarding straining were improved to a similar extent by dutasteride and combined therapy. Overall, these results are in agreement with the primary 4-year analysis of the CombAT study, which found combined therapy to be significantly better than either monotherapy in reducing total IPSS scores [16]. Furthermore, these results confirm and extend findings from the previous 2-year *post hoc* analysis of IPSS storage and voiding subscale data [18].

An interesting aspect of the present analysis of CombAT is that dutasteride monotherapy performed significantly better than tamsulosin monotherapy in reducing both voiding and storage symptoms from 27 months until the final analysis at 4 years. These results build upon those of the previous 2-year *post hoc* analysis of CombAT, which found dutasteride to be significantly better than tamsulosin in reducing voiding symptoms, but only equally as efficient as tamsulosin in reducing storage symptoms [18]. The observations in this 4-year analysis could be due to sustained improvements with dutasteride, a reduction in the efficacy of tamsulosin over this period or, more likely, a combination of both these factors. Unlike 5ARIs, α-blockers do not reduce prostate volume and can only act to reduce tone in smooth muscle and relieve LUTS as far as existing BOO allows [21]. In the primary 4-year analysis of the CombAT study, it was postulated that the observed reduction in symptom benefit in the tamsulosin group may have been driven by unchecked prostate volume increases that were observed in this treatment arm during the study [16]. However, tamsulosin does continue to contribute to long-term symptom benefits when used in combination, as highlighted by the difference in symptom improvement between combined therapy and dutasteride monotherapy at 4 years. Other trials have also shown that α-blockers can retain the ability to delay progression of LUTS symptoms over the long term [12], and it is likely that the effectiveness of combined therapy is due in part to 5ARI-driven reductions in prostate volume enhancing the therapeutic benefits that can be gained with α-blocker therapy.

As discussed previously, the improvement in storage symptoms at 2 years was similar in the dutasteride and tamsulosin monotherapy groups [18]. In the present analysis, dutasteride was better than tamsulosin at improving storage symptoms from 27 months onwards. These findings provide further evidence to support the hypothesis that storage symptoms arise from maladaptive remodelling of bladder

structure and function, which are driven by BOO [4]. Alleviation of BOO (and hence storage symptoms) may therefore result from the progressive reduction in prostate volume with dutasteride [17]. The long-term superior efficacy of dutasteride compared with tamsulosin shown by the present analysis supports the primary 4-year CombAT analysis in which combined therapy was significantly better than tamsulosin, but not dutasteride, in reducing relative risk of AUR and BPH-related surgery [16].

An interaction between therapy response and baseline prostate volume was noted in the *post hoc* 2-year analysis of CombAT storage and voiding data [18]. For this reason, data at 4 years were also stratified by baseline prostate volume. Among men with baseline prostate volumes within the bottom two tertiles, combined therapy was significantly better at reducing both storage and voiding subscores than either monotherapy. In contrast, improvements in storage and voiding subscores in the upper prostate volume tertile (≥58 mL) were not significantly different between the combined therapy and dutasteride groups, although both combined therapy and dutasteride monotherapy were significantly more effective than tamsulosin alone. Based on the finding of no significant difference between combined therapy and dutasteride monotherapy in men with a prostate volume of ≥58 mL, it is possible that the effectiveness of tamsulosin is reduced in men with larger prostates, and that the prostate volume-reducing action of dutasteride brings greater relief for these patients. Nevertheless, this analysis has shown that long-term combined therapy with the α-blocker (tamsulosin) plus the 5ARI (dutasteride) improves storage and voiding symptoms in men with a prostate volume of ≥30 mL. Tamsulosin acts to rapidly improve storage and voiding symptoms, although such improvements are not wholly sustained, while dutasteride improves storage and voiding symptoms more gradually and with sustained effect. The combination of these two agents thus provides rapid and sustained improvement of both categories of LUTS.

CombAT is the first study to report the effects of combined therapy on storage and voiding subscales of the IPSS. While these subscales have been shown to have psychometric validity [22], an analysis of data from a USA Veterans Affairs study, in which men with BPH received either finasteride alone, terazosin alone, finasteride plus terazosin, or placebo, concluded that separation of LUTS into voiding and storage domains was not clinically useful [20]. However, that study was limited by its relatively short duration (1 year) and by the fact that it did not detect a significant effect of finasteride on symptoms compared with placebo. The other long-term study of combination therapy, the Medical Therapy of Prostatic Symptoms (MTOPS) study, has not reported on how storage and voiding symptoms are affected by treatment (finasteride alone, doxazosin alone, finasteride plus doxazosin, or placebo) [17]. The CombAT study also differs from MTOPS as the patients studied were at risk of BPH progression by virtue of having a prostate volume of ≥30 mL and a PSA level of at least 1.5 ng/mL.

In conclusion, in men with a prostate volume of ≥30 mL, combined therapy with dutasteride plus tamsulosin provided better long-term (up to 4 years) control of both storage and voiding LUTS compared with tamsulosin monotherapy. Combined therapy was better than dutasteride monotherapy in men with a prostate volume of ≥30 to <58 mL, but not in men with a prostate volume of ≥58 mL.

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## CONFLICT OF INTEREST

Francesco Montorsi and Claus Roehrborn have acted as Advisors to GSK. Paul Gagnier and Timothy H. Wilson are Employees of GSK.

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Abbreviations: **BPE**, benign prostatic enlargement; **OAB**, overactive bladder; **5ARI**, 5α-reductase inhibitor; **AUR**, acute urinary retention; **CombAT**, Combination of Avodart and Tamsulosin (study); **HRQL**, health-related quality of life; **MTOPS**, Medical Therapy of Prostatic Symptoms (study).

## EDITORIAL COMMENT

### THE EFFECTS OF DUTASTERIDE OR TAMSULOSIN ALONE AND IN COMBINATION ON STORAGE AND VOIDING SYMPTOMS IN MEN WITH LOWER URINARY TRACT SYMPTOMS (LUTS) AND BENIGN PROSTATIC HYPERPLASIA (BPH): 4-YEAR DATA FROM THE COMBINATION OF AVODART AND TAMSULOSIN (CombAT) STUDY

The above study confirms the benefits of combined drug therapy with a 5α-reductase inhibitor (5ARI) and an α-blocker compared with either of these drugs as monotherapy in relieving both storage and voiding symptoms in men with prostates ≥30 mL and with moderate-to-severe LUTS. α-blockers have generally been considered being the more beneficial of the two classes of drugs in treating the storage symptoms although this thought was not supported by the 2-year *post hoc* analysis of the CombAT study where monotherapy with dutasteride was found to be equally effective to tamsulosin [1]. The present study now shows that given enough time, 5ARIs (such as dutasteride) have a meaningful role to play in reducing storage symptoms and to a greater extent than α-blockers. This is of relevance given that as urologists, we are all familiar with the man who presents to our offices with LUTS, complaining predominantly about the storage rather than voiding symptoms; hence, it is important to understand how drug therapy influences these categorisations of LUTS.

This study contributes to the standard of care shifting towards combined drug therapy in appropriately selected patients, but at the same time, better defining the role of the α-blockers. We already know that they work well as monotherapy for men with LUTS and smaller prostates [2]. For the men with larger prostates (>58 mL), these results would perhaps support the cessation of an α-blocker beyond 27 months. From a practical perspective, this is probably not going to happen as it is simply easier to keep a man on combined therapy if already satisfied with treatment and even more so if the fixed-dose combined drugs, which have recently become available, are prescribed.

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## REFERENCES

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2 **Roehrborn CG, Van Kerrebroeck P, Nordling J.** Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three doubleblind, placebo-controlled trials. *BJU Int* 2003; **92**: 257–61